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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,242	11/29/2001	Erwin Bischoff	Le A 33 535	1312

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EXAMINER
ANDERSON, REBECCA L

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,242	BISCHOFF ET AL.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-6,8-16 and 21-62 is/are pending in the application.

4a) Of the above claim(s) 6,9-15,25-29,40,41 and 57-62 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-5,8,16,21-24,30-39 and 42-56 is/are rejected.

7)☒ Claim(s) 1-5, 8, 16, 21-24, 30-39 and 42-56 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 others
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-6, 8-16 and 21-62 are currently pending in the instant application. Claims 6, 9-15, 25-29, 40, 41 and 57-62 are withdrawn from further consideration as being drawn to a non-elected invention (it is noted that claim 41 is dependent on a cancelled claim which is drawn to non-elected subject matter). Claims 42-56 are rejected and claims 1-5, 8, 16, 21-24, 30-39 and 42-56 are provisionally rejected.

Election/Restrictions

Applicant's election with traverse of Group IV, as found on page 1 of the response to the restriction requirement filed 4 June 2003 is acknowledged. As mentioned by applicant's representative, it is correct that the definition of the group IV, should include R7 as defined in claim 1. Furthermore, upon reconsideration, the definition of group IV has been expanded to include R3 as naphthly group optionally sutbstituted as defined in claim 1. Therefore, Group IV is drawn to products of the formula I, wherein:

A is CH, D is CH, E is CH, G is CH, R^1 is CO-NR^4R^5, R^2 is piperazinyl, wherein one of the nitrogen atoms in the piperazinyl is substituted by R7 and the piperazinyl is also optionally substituted by one to three hydroxyl groups and/or by a radical of the formula –NR8R9, R^3 is phenyl or naphthyl optionally substituted as found in claim 1, L^1, L2, R4, and R5 are as in claim 1,R8 and R9 are identical or different and each represents hydrogen, (C1-C6)-alkyl or (C3-C7)-cycloalkyl, and processes for their preparation, and their methods of use.

Claims 1-5, 8, 16, 21-24, 30-39 and 42-56 are considered to read on the subject matter of the elected group. Claims 6, 9-15, 25-29, 40, 41 and 57-62, which are not drawn to the elected group as mentioned above, are withdrawn from further consideration as being drawn to a non-elected invention.

Applicant's traversal of the Lack of Unity requirement is on the ground(s) that the examiner has misinterpreted the rules concerning unity of invention in the context of a Markush claim and has incorrectly identified the technical feature in common with each of the inventions. Applicant also provides a structure on page 3 of the response to the restriction requirement which applicant considers the special technical feature that defines a contribution which each of the inventions, considered as a whole, makes over the prior art. This is not found persuasive because the claims herein lack unity of invention under PCT rule 13.1 and 13.2 since the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art and the alternatives (the substituents) on the common structure do not all belong to an art recognized class of chemical compounds (i.e. R2 can contain a morpholine, a piperazine or an alkyl group). The compounds claimed contain a cyclohexyl benzimidazole, which does not define a contribution over the prior art (as can be seen by the compounds on page 4 of EP 0 725 064 A1). The substituents on the cyclohexyl benzimidazole vary extensively and when taken as a whole result in vastly different compounds. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper. Additionally, even if the structure on page 4 of

applicants response was the technical feature that all of the inventions have in common, this would still not be a special technical feature that defines a contribution which each of the inventions, considered as a whole, makes over the prior art because this feature is well known in the art as can be seen by US Patent No. 5, 395, 840 (columns 24) and US Patent No. 5, 935, 983 (column 2). Applicant does not dispute the examiner's conclusion that claims 14 and 15 lack unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,

6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention is the treatment or prevention of any disorder in a mammal, with dependent claims 43, 46, 49, 52, and 55 drawn specifically to ischaemic disorder of the cardiovascular system.

The State of the Prior Art

The state of the prior art is that there is no one compound that is capable of the treatment or prevention of any and all disorders in a mammal. There are many factors to consider for the treatment or prevention of disorders in mammals such as the inhibition or activation of different receptors, the internal environment of the cell and how certain compounds will mediate different pathways .

The Predictability or Lack Thereof in the Art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic and preventive effects on any disorder in a mammal is dependent on many conditions such as the chemical pathways present, what receptors are inhibited or activated and what the internal environment of the cell is.

Hence, in the absence of a showing of correlation between any and all disorders of a mammal including the treatment or prevention of ischaemic disorder of the cardiovascular system with the inhibition of adenosine uptake as discussed in the specification and in the absence of convincing examples of the affect of the inhibition of adenosine uptake on the treatment of any disorder in a mammal including ischaemic disorder of the cardiovascular system, one of skill in the art is unable to fully predict possible results from the administration of the compounds as instantly claimed. of the

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The Amount of Direction or Guidance Present

The direction present in the instant specification is that the compounds of claim 1 can treat or prevent any disorder in a mammal, specifically, ischaemic disorder of the cardiovascular system. However, besides the initial paragraph stating the correlation between adenosine uptake inhibition and certain ischaemic disorder, the specification is silent and fails to provide guidance as to whether all disorders, including ischaemic disorder of the cardiovascular system, of a mammal are related to the inhibition of adenosine uptake and whether causing the inhibition of adenosine uptake would provide treatment or prevent the disorders. In regards to ischaemic disorders

specifically, the specification provides an example for the treatment of peripheral ischaemia, but this example fails to provide data that shows the improvement in circulation to support the statement of a significant improvement of the circulation of the ischaemic hind leg.

The Presence or Absence of Working Examples

The only working examples present in the instant specification is in vitro testing for the inhibition of adenosine uptake, in vivo testing for adenosine-reuptake inhibitors and in vivo testing in mouse angiogenesis model. For the in vitro testing for the inhibition of adenosine uptake, there is no evidence in the specification as to how this would provide a beneficial effect towards the treatment or prevention of any disease including ischaemic disorder of the cardiovascular system. In regards to the in vivo testing for adenosine-reuptake inhibitors, this example fails to provide the results of the test and therefore does not provide any evidence that the compounds as claimed would provide any beneficial effect towards the treatment or prevention of any disease including ischaemic disorder of the cardiovascular system. Finally, in regards to the mouse angiogenesis model, this example, which provides a statement as to how adenosine-reuptake inhibitors significantly improve the circulation of the ischaemic hind leg in comparison with the corresponding controls, fails to provide the results of the test to support this conclusion and therefore does not provide evidence as to how the compounds as instantly claimed would provide a beneficial effect towards the treatment or prevention of any disease including ischaemic disorder or the cardiovascular system.

The Breadth of the Claims

In the instant case, the breadth of the claims is vary broad and is the treatment or prevention of any disorder in a mammal with the compound as instantly claimed.

Quantity or Experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what disorders in mammals would benefit from the inhibition of adenosine uptake and then determine what compounds as claimed would provide this benefit. One of skill in the art would then have to perform undue experimentation to determine whether the compounds would treat or prevent the disorder.

The Level of the Skill in the art.

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which disorders would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound as instantly claimed for the treatment or prevention of any disorder in a mammal. As a result necessitating one of skill to perform an exhaustive search for which disorders can be treated or prevented by the compound as instantly claimed in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation with no assurance of success.

This rejection can be overcome deleting claims 42-56.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 8, 16, 21-24 and 30-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 11 and 15-18 of copending Application No. 09980242. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Applicant's instant claims 1-5, 16, 21-24 and 36-39 are directed to products of the general formula (I) wherein A, D, E and G are CH, R1 is C(O)-NR4R5 wherein R4 and R5 are H or (C1-C6)alkyl, R2 is 4-R7-piperazin-1-yl, R7 is H, (C1-C6)alkyl, etc., R3 is optionally substituted phenyl or naphthyl and L1 and L2 are hydrogen, halogen hydroxyl, carboxyl, etc, its salt, prodrug, hydrate and stereoisomers. Claim 8 and claims 30-35 are drawn to a process for preparing compounds of the general formula (I) using the compounds of formulas (II), (III), (IV), (V) and (VI) or (IIIa), (VII), (VIII), (IX) and (X) specifically wherein T represents methyl or ter-butyl (claim 30), V represents halogen, mesylate, or tosylate or bromine (claims 31-32), formula V is carbonyl halide, carboxylic anhydride or carboxylic ester (claim 33), Y is chlorine or bromine in formula IIIa (claim 34) and the step of converting the compound of formula I into the corresponding salts is carried out by a reaction with an acid (claim 35).

Copending Application No. 09980243 claims 1-5, 11 and 15-18 are directed to products of the general formula (I) wherein A, D, E and G are CH, R1 is C(O)-NR4R5

wherein R4 and R5 are H or (C1-C6)alkyl, R2 is 4-R7-piperazin-1-yl, R7 is H, (C1-C6)alkyl, etc., R3 is optionally substituted phenyl or naphthyl and L1 and L2 are hydrogen, halogen hydroxyl, carboxyl, etc. and its salt. Claim 4 specifically discloses (S)-N-{{(1R,2R)-2-{4-{[2-(4-Methyl-piperazin-1-yl)-benzimidazol-1-yl]methyl}-phenyl}-cyclohex-1-yl} carbonyl}-phenylglycinamide. Claim 5 and claims 15-18 are drawn to a process for preparing compounds of the general formula (I) using the compounds of formulas (II), (III), (IV), (V) and (VI) or (IIIa), (VII), (VIII), (IX) and (X). Claims 15-18 limit the substituents on the compounds, i.e. T is methyl or tert-butyl, V is halogen, mesylate or tosylate, V is bromine, and Y is chlorine or bromine. The process of claim 5 includes that the corresponding salts can be prepared by reaction with an acid.

The difference between the instant claims and the claims of copending Application No. 09980243 is that the product claims of copending application No. 09980243 are only drawn to the compounds and their salts.

However, it would have been obvious to someone of ordinary skill in the art, when faced with the co-pending Application No. 09980243 to prepare compounds in their salt form when the co-pending application discloses on page 4, the preferred salts and that the compound of the invention can occur in different stereoisomeric forms, and the specification also discloses the hydrochloric acid salt on page 37 which is also a specific stereoisomer. Therefore the claims at issue, while including prodrugs, hydrates, and stereoisomers along with the compound and its salt, are considered obvious over the claims of co-pending Application No. 09980243 since co-pending application discloses preferences to specific salts and stereoisomers. Therefore, the

instant claims and the claims of copending Application No. 09980243 are considered provisional obvious type double patenting. The motivation to make the instantly claimed compounds is to prepare other compounds that are useful for the treatment of ischeamic braid disorders.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

Claims 1-5, 8, 16, 21-24, 30-39 and 42-56 are objected to as containing non-elected subject matter, but would appear allowable if rewritten to include only the elected subject matter as mentioned above as the elected Group IV, rewritten to overcome the 35 U.S.C. 112 1st paragraph rejections and rewritten to overcome the provisional obvious type double patenting rejection or providing a terminal disclaimer to overcome the provisional obvious type double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (703) 605-1157. Mrs. Anderson can normally be reached Monday through Friday 7:00AM to 3:30PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (703) 308-4537.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone numbers are (703) 308-1235 and (703) 308-0196.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4242, (703) 305-3592, and (703) 305-3014.

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